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Adenocarcinomas of the oral cavity:
A clinicopathologic study of terminal duct carcinomas

by

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Introduction

The reported incidence of malignant salivary gland tumors in the oral cavity has varied according to the referral pattern of the authors' institution (Chaudhry *et al.,* 1961; Epker and Henny, 1969; Fine *et al.,* 1960; Luna *et al.,* 1968; Vellios and Shafer, 1959) (Table I). It is reasonable to assume, however, that there is a nearly equal incidence of benign and malignant variants. Of a total of 1,965 oral salivary gland tumors, 52 per cent were classified as benign and 48 per cent as malignant (Gates, 1972). Forty-two per cent of the latter were adenoid cystic carcinomas. Mixed tumors (pleomorphic adenomas) made up 92 per cent of the benign tumors. Such a numerical dominance by these two types of salivary gland neoplasia has led to their use as paradigms and, in the event, has obscured recognition and reporting of other, less often encountered neoplasms, e.g. the adenocarcinomas.

A clinico-pathologic evaluation of adenocarcinomas of salivary tissues has also been delayed by their inclusion under the generic heading of 'adenocarcinoma', wherein all forms of glandular malignancy are included, or by being placed in the category of 'adenocarcinoma, not otherwise specified'. Adenocarcinomas are, however, distinctive neoplasms which may be sub-classified according to their tissue growth patterns or histo-cytomorphology. Table II presents a classification of adenocarcinoma which is applicable to both major or minor salivary glands.

In this report, we present a study of 12 patients with a hitherto undescribed variant of adenocarcinoma of the oral cavity—*the terminal duct carcinoma.*

Report of Cases

A summary of the 12 cases is presented in Table III. Eleven of the 12 were from the consultation service of the senior author. Case 4 represents a patient treated at The University of Texas M. D. Anderson Hospital. Eight of the patients were women. The age of the patients at the time of surgery ranged from 26 to 65 years. Two patients (cases 3 and 5) gave a history of an antecedent lesion removed from the palate 12 and 8 years earlier.

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TABLE I
FREQUENCY OF MALIGNANCY OF INTRAORAL SALIVARY GLAND TUMORS

Authors	No. of tumors	Per cent malignant
Vellios and Shafer (1959)	54	54
Fine *et al.* (1960)	79	47
Chaudhry *et al.* (1961)	94	54
Epker and Henny (1969)	90	70
Luna *et al.* (1968)	68	81

The palate, usually at the junction of the soft and hard palate, was the primary site in five patients.

The clinical presentation was that of a painless mass, covered with an intact mucosa in all patients. The size of the tumors ranged from 1.5 cm. to 5.0 cm. in major dimension. The largest tumor presented in the base of the tongue.

TABLE II
HISTOPATHOLOGIC CLASSIFICATION OF ADENOCARCINOMAS OF SALIVARY TISSUES

Papillary adenocarcinoma (with or without mucus production)
Mucoid (colloid) adenocarcinoma
Clear cell carcinomas (epithelial-myoepithelial carcinoma of intercalated duct origin)
Ductal carcinomas
Terminal duct carcinomas
Poorly differentiated and undifferentiated adenocarcinoma
Neuroendocrine carcinomas
(a) Adenocarcinoma with neuroendocrine differentiation
(b) 'Oat cell', carcinoid

A form of salivary gland adenoma was the original histopathologic diagnosis in 7 of 12 tumors. A diagnosis of adenoid cystic carcinoma was made in three patients. In every instance, the contributing pathologist expressed doubt over his diagnosis.

Surgical excision was the primary treatment in all patients. The extent of the excision ranged from 'excisional biopsy' to a bloc resection, including hemimandibulectomy in three patients (cases 8, 9 and 10). Four patients (cases 1, 6, 8 and 10) also underwent a radical neck dissection. No histologically positive nodes were found. Two patients received post-operative irradiation (cases 1 and 10).

Invasion of bone was evident in three cases and presumed in one.

All of the patients are alive and without clinical recurrence of their neoplasm, but the follow-up period has been short; one month to two and one-half years.

Histopatholgic Findings

The light-optic appearance of the terminal duct adenocarcinomas was remarkably similar in all cases. Figures 1–6 are not only representative, they are prototypical.

A deceptive circumscription was present in nearly every case but a complete capsule was never present. An infiltrative growth pattern was always present. Infiltration was either by single ducts (particularly beneath the mucosa or into adjacent salivary tissue) or by groups of neoplastic ducts and solid epithelial

TABLE III
SUMMARY OF CASES

Case	Sex-age	Site	Original diagnosis	Invasion of nerve	Invasion of bone
1.	F-47	Palate	Adenoid cystic carcinoma	+	—
2.	M-56	Palate	*Malignant mixed tumor*	+	—
3.	F-46	Palate	Pleomorphic adenoma	+	+
4.	F-49	Palate	Adenoid cystic carcinoma	+	—
5.	F-26	Palate	Monomorphic adenoma	+	—
6.	M-59	Base of tongue	Monomorphic adenoma	+	—
7.	M-38	Base of tongue	Monomorphic adenoma	+	—
8.	F-32	Posterior trigone	Monomorphic adenoma	+	+
9.	F-41	Retromolar pad	Adenocarcinoma	+	—
10.	M-63	Anterior mandibular mucosa	Adenoid cystic carcinoma	+	+
11.	F-39	Upper lip	Monomorphic adenoma	+	—
12.	F-65	Buccal mucosa	Monomorphic adenoma	+	—

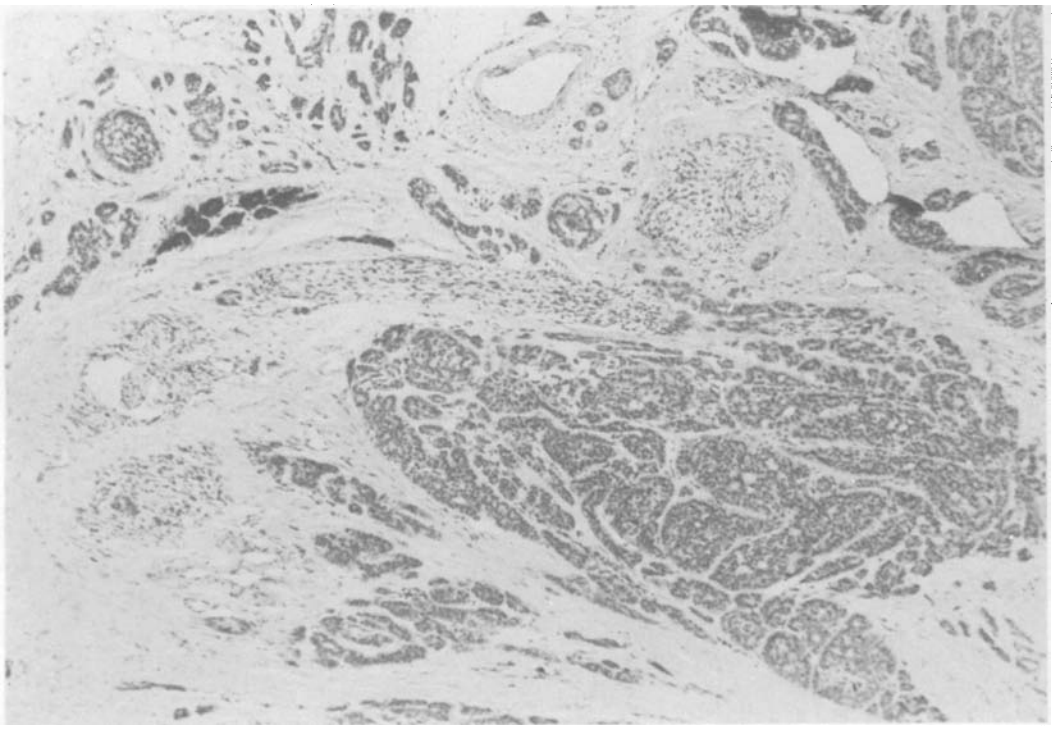

FIG. 1

Intraoral terminal duct carcinoma. Note the apparent multifocal origin and relation to nerves. Hematoxylin and eosin ×20.

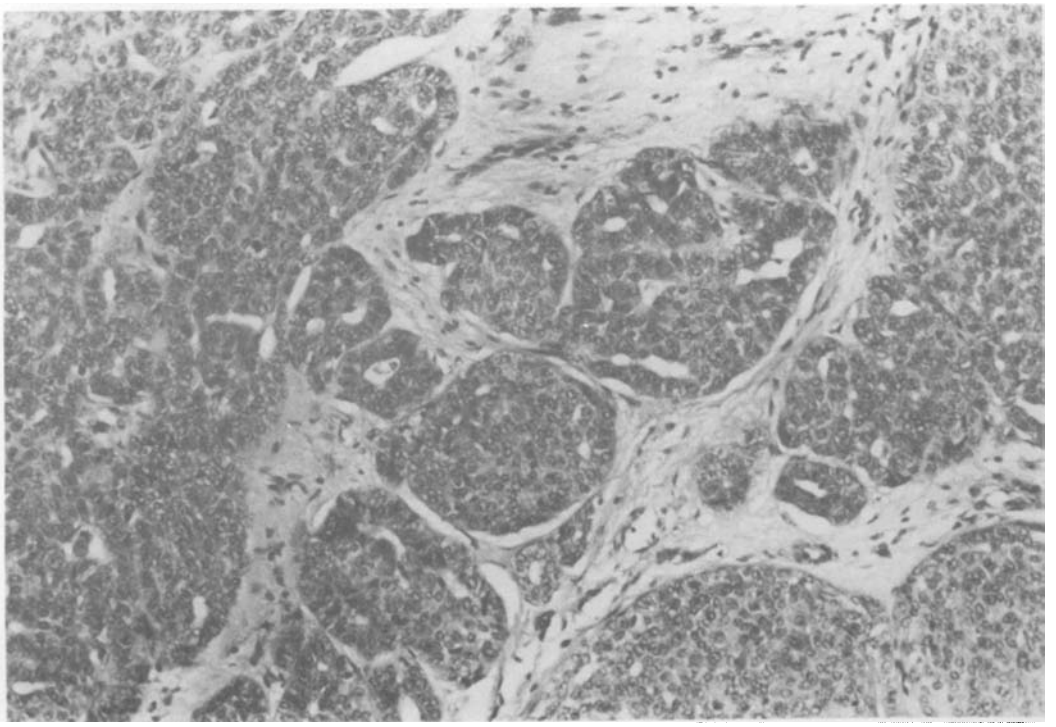

FIG. 2

Ductular and solid epithelial components of terminal duct carcinoma. Hematoxylin and eosin ×200.

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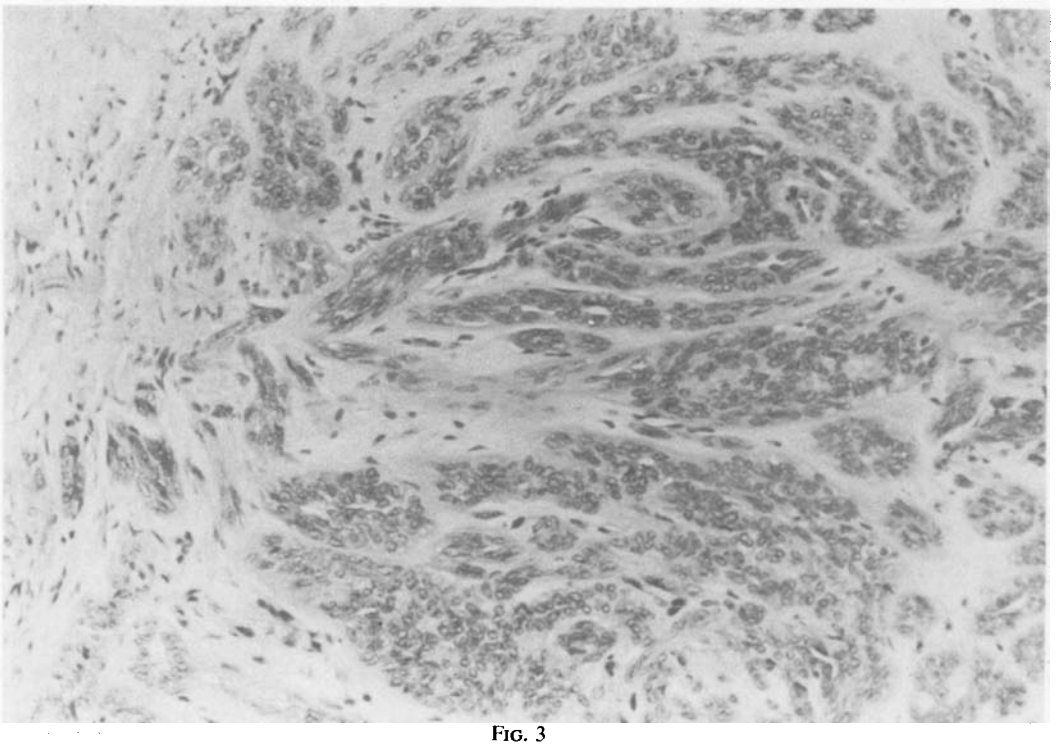

FIG. 3

Small ducts, spindle cells, and characteristic interepithelial stroma found in terminal duct carcinomas. Hematoxylin and eosin ×250.

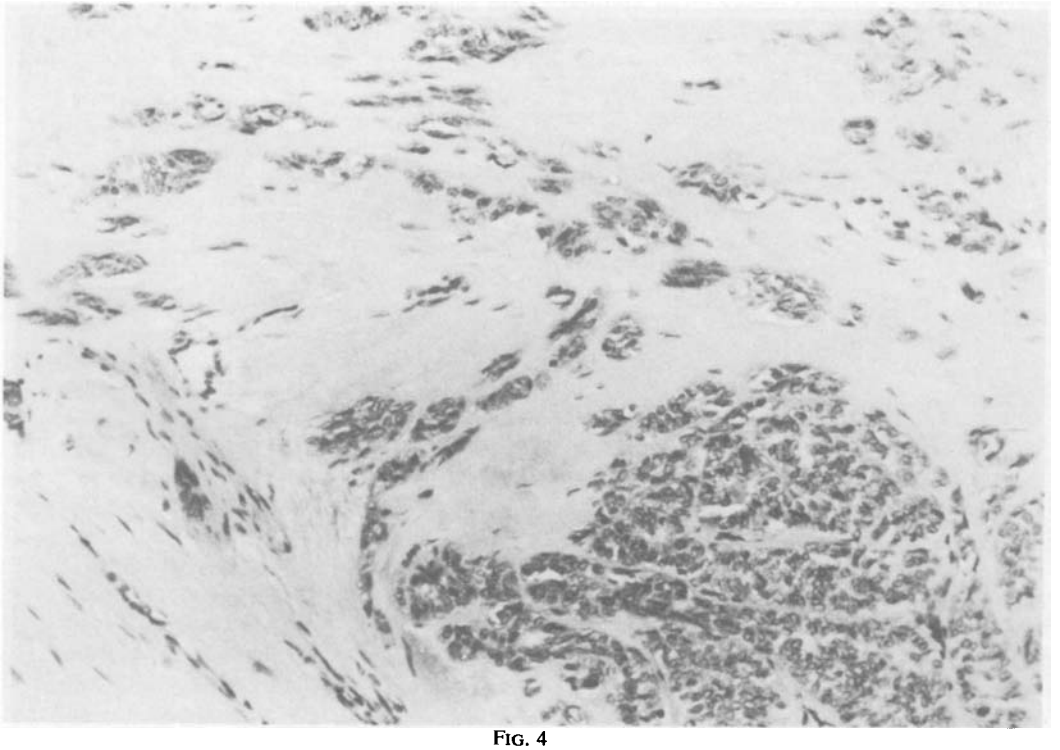

FIG. 4

Typical mucohyaline stroma that is found in areas of a terminal duct carcinoma. Hematoxylin and eosin ×180.

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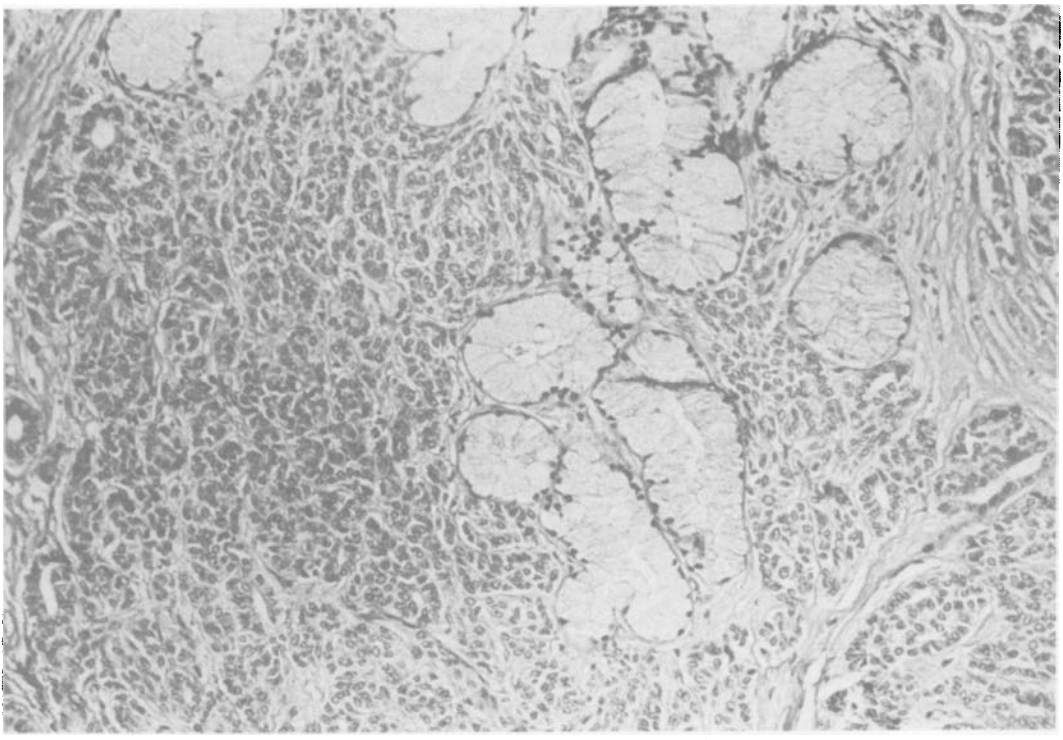

FIG. 5
Invasion of normal mucinous acini by terminal duct carcinoma. Hematoxylin and eosin ×180.

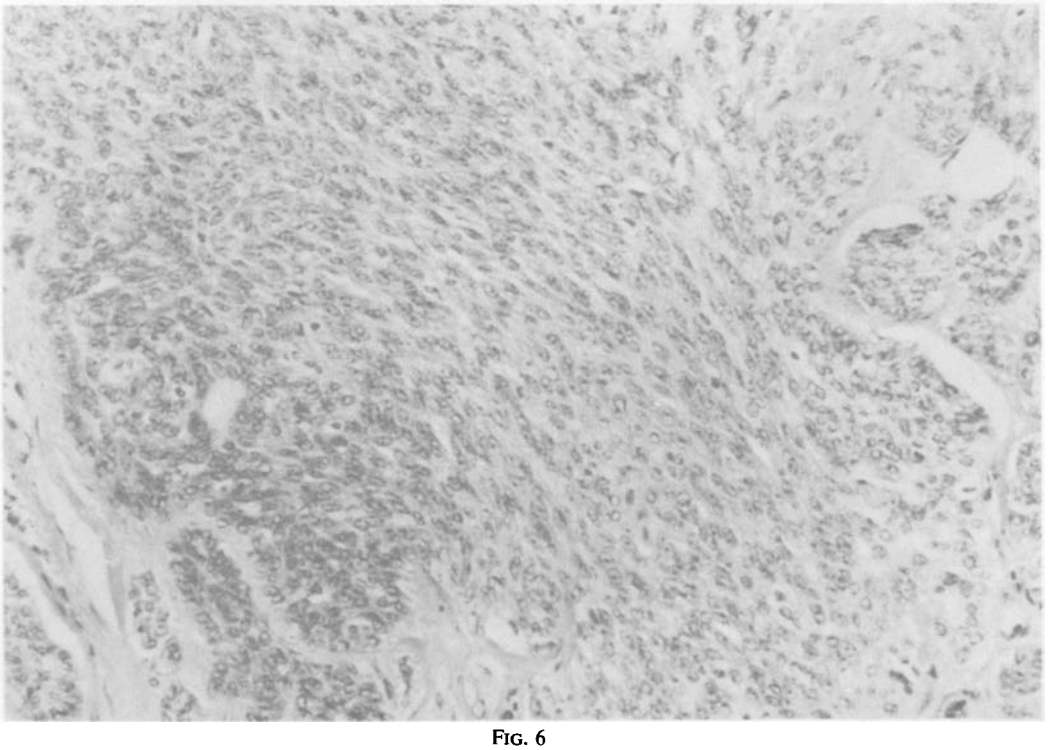

FIG. 6
Spindle cell area in a terminal duct carcinoma. By light optic and electron optic study, the cells manifest myoepithelial differentiation. Hematoxylin and eosin ×200.

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nodules (Figs. 5 and 7). Neurotropism, manifested by perineural, perineurial, and intraneural extension by the neoplasm was especially prominent (Fig. 8). All 12 neoplasms demonstrated these findings. Invasion into adjacent bone (hard palate and mandible) was present in two cases (Fig. 9).

The neoplastic cells were arrayed either as small ducts with a single cell lining or as solid masses. In some microscopic fields, the ducts were closely apposed; in other fields, a mucohyaline or eosinophilic hyaline stroma separated the ducts (Fig. 4).

A histologic feature, present in varying degrees, in all of the tumors, was an elongation or spindling of the neoplastic cells (Figs. 3 and 6). These cells, at times, formed micronodules reminiscent of a circumferential perineural aggregation. Except for the spindle areas, the epithelial cells manifested a uniformity and regularity in cell size, shape and nuclei. In keeping with an over-all rather benign cytologic character, mitoses were scarce or absent (Fig. 2).

Discussion

Removal of salivary adenocarcinomas from loosely defined or even inappropriate histologic categories will allow a clearer assessment of their frequency and biologic behavior (Stene and Koppang, 1981). Their predominance among non-epidermoid tumors in the sinonasal tract may be seen in

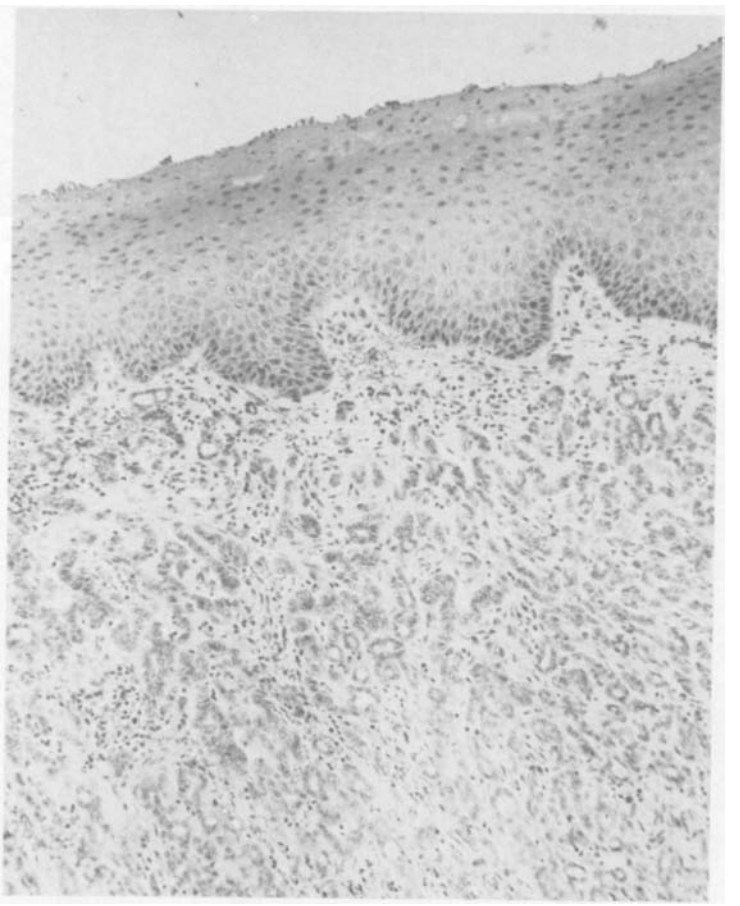

FIG. 7
Terminal duct carcinoma infiltrating beneath squamous mucosa of the palate. Hematoxylin and eosin ×80.

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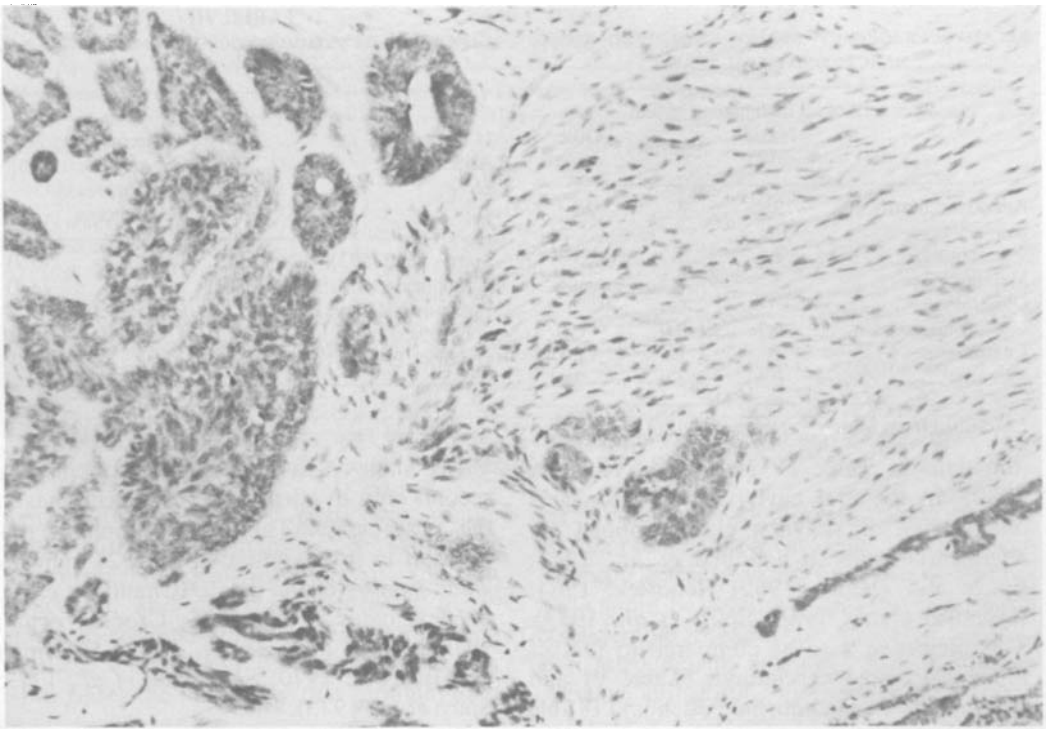

FIG. 8

Terminal duct carcinoma of oral cavity invading a medium-sized nerve. Hematoxylin and eosin ×200. This microscopic finding was present in all cases of this series.

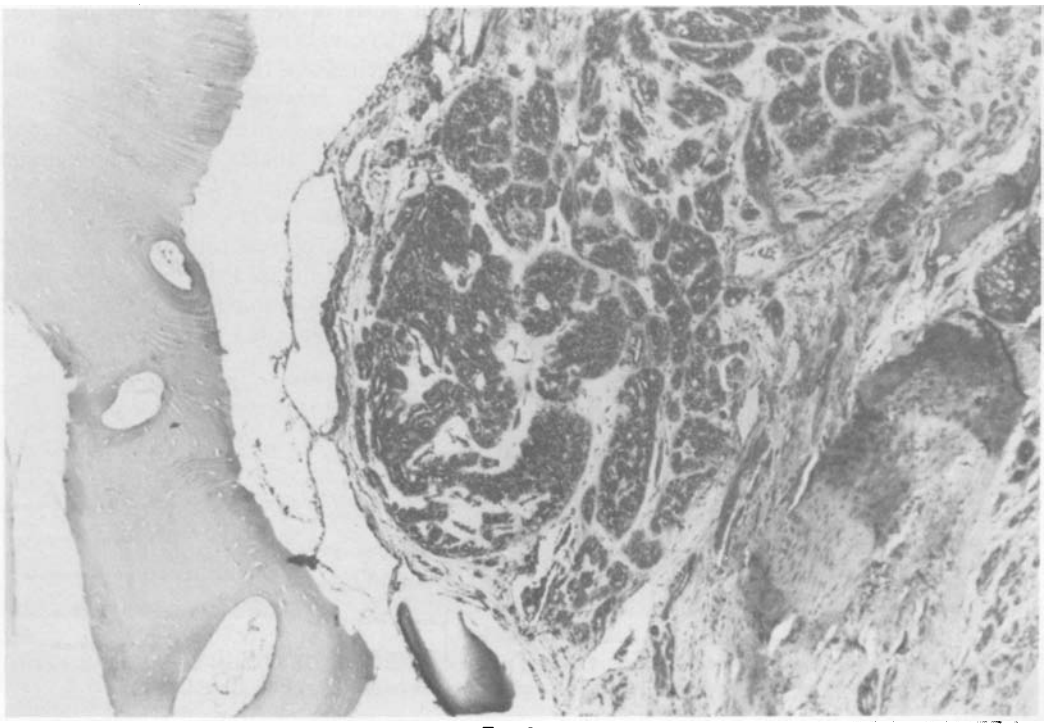

FIG. 9

Bone of the mandible invaded by terminal duct carcinoma. Hematoxylin and eosin ×80.

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TABLE IV
RELATIVE FREQUENCY OF NON-EPIDERMOID MALIGNANCY: SINO-NASAL TRACT*

	Per cent of all malignancy at site		
	Nasal cavity	Antrum	Other sinuses
Adenocarcinoma	9	6	20
Salivary type carcinoma	1.3	1.7	3.3
Melanoma	3	0.5	0.8
Olfactory neuroblastoma	0.7	0.0	0.0
Lymphoma	2	1.6	2.1
Sarcoma	2.6	2.9	2.5

* Modified from Muir and Nectoux (1980).

the data in Table IV (Muir and Nectoux, 1980). In the oral cavity (Table V) nearly one-quarter of salivary gland tumors are adenocarcinomas (Chaudhry *et al.*, 1961; Epker and Henny, 1969; Hendrick, 1964; Reynolds *et al.*, 1966; Spiro *et al.*, 1973). This incidence is to be compared to that of mucoepidermoid carcinomas (Table VI and carcinomas ex pleomorphic adenoma (Table VII). Such data place adenocarcinomas second only to adenoid cystic carcinomas in the oral cavity. Table VIII amplifies this position in its presentation of 1221 salivary gland tumors of the palate (Chaudhry *et al.*, 1961; Coates *et al.*, 1975; Crocker *et al.*, 1970; Epker and Henny, 1969; Hjertman and Eneroth, 1970; Soskolkne *et al.*, 1973; Spiro *et al.*, 1973).

TABLE V
ADENOCARCINOMA OF THE ORAL CAVITY

Authors	No. salivary gland tumors	No. adeno-carcinomas	(%)
Spiro *et al.* (1973)	345	92	(27)
Chaudhry *et al.* (1961)	94	27	(18)
Epker and Henny (1969)	90	26	(18)
Hendrick (1964)	44	10	(23)
Reynolds *et al.* (1966)	31	6	(20)
	604	141	(23)

TABLE VI
MUCOEPIDERMOID CARCINOMAS OF THE ORAL CAVITY

Authors	No. salivary gland tumors	No. muco-epidermoid carcinomas	(%)
Spiro *et al.* (1973)	345	55	(13)
Chaudhry *et al.* (1961)	94	10	(10.6)
Epker and Henny (1969)	90	3	(15.5)
Hendrick (1964)	44	3	(7)
Reynolds *et al.* (1966)	31	4	(13)
	604	86	(14.2)

TABLE VII
CARCINOMA EX PLEOMORPHIC ADENOMA OF THE ORAL CAVITY

Authors	No. salivary gland tumors	No. carcinomas ex pleo-morphic adenoma	(%)
Spiro *et al.* (1973)	345	11	(3.2)
Chaudhry *et al.* (1961)	94	3	(3.2)
Epker and Henny (1969)	90	0	(0)
Hendrick (1964)	44	8	(18)
	573	22	(4.0)

The majority of the *adenocarcinomas* of salivary tissues are presumed to arise from the reserve cells of the metabolically active or conduit parts of the salivary duct unit, i.e., intra-, inter-, and excretory ducts (Fig. 10). The histogenesis of the terminal duct adenocarcinomas, however, resides in the neoplastic expression of the reserve cells of the intercalated ducts; sharing this origin with the tumors listed in Figure 10 (Batsakis, 1980b; Eversole, 1971).

Within the group of tumors arising from the intercalated ducts, there is a rather wide range of biologic behavior, but the clinical course of terminal duct adenocarcinomas is

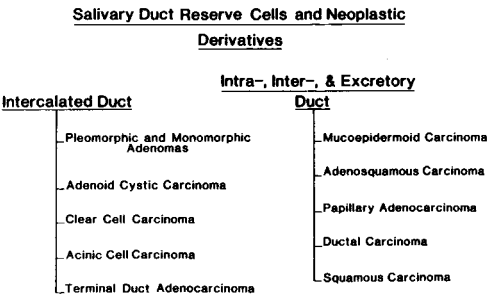

FIG. 10

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TABLE VIII
SALIVARY TUMORS OF PALATE: HISTOLOGIC CLASSIFICATION*

Histologic type	Number of tumors	Per cent	Per cent of total
Benign	*625*		
Mixed tumor	573	92	47
Others	52	8	4.2
Malignant	*596*		
Adenoid cystic carcinoma	274	46	22
Adenocarcinoma	143	24	12
Mucoepidermoid carcinoma	120	20	10
Carcinoma ex pleomorphic adenoma	45	7.5	3.7
Acinous cell carcinoma	7	1.2	0.6
Undifferentiated	7	1.2	0.6
Miscellaneous	—	0.1	—

* Data assembled from the reports by Chaudhry *et al.*, 1961; Coates *et al.*, 1975; Crocker *et al.*, 1970; Epker and Henny, 1969; Hjertman and Eneroth, 1970; Soskolne *et al.*, 1973; Spiro *et al.*, 1973.

akin to that of adenoid cystic carcinoma. Both carcinomas manifest a significant neurotropism, local invasion of adjacent structures, and a low incidence of metastases to regional lymph nodes. The sharing of these clinical and pathologic characteristics raises the possibility that terminal duct carcinomas are only histopathologic variants of adenoid cystic carcinomas. This has been carefully considered by the present authors and cannot be confirmed. Although there is a considerable breadth of histologic expression attributed to adenoid cystic carcinoma (tubular, cribriform, cylindromatous, solid),

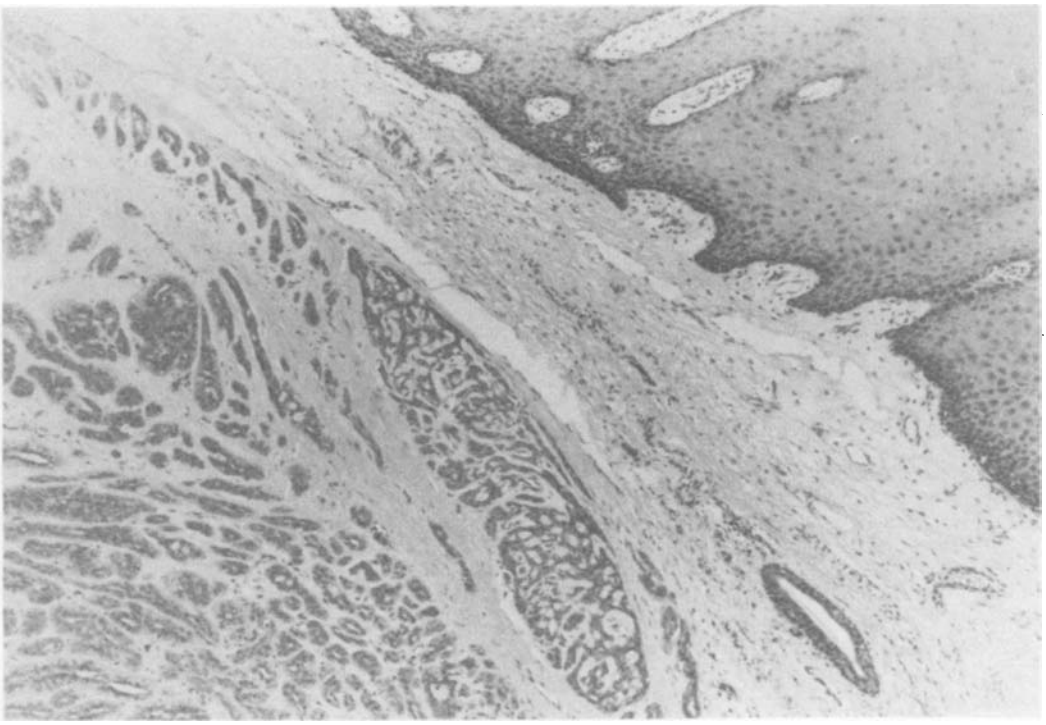

FIG. 11

Focally circumscribed terminal duct carcinoma beneath palatal mucosa. Superficial biopsy specimen from areas such as this can be misdiagnosed as a pleomorphic adenoma. Hematoxylin and eosin ×80.

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none of the terminal duct carcinomas could be placed within the spectrum.

As judged by the original diagnoses, monomorphic and pleomorphic adenomas posed problems in differential diagnosis. Indeed, superficial biopsy specimens containing lobules with a mucohyaline matrix can simulate adenomas (Fig. 11). The often deceptively benign cytomorphology of the cells and their ductal arrangement may also mislead the examiner to a diagnosis of monomorphic adenoma (Batsakis *et al.*, 1981). Peripheral infilitrative growth, spindle cell areas and most of all, invasion of nerves, eliminate a diagnosis of monomorphic adenoma.

The authors have seen a similar small duct carcinoma as the malignant component of some carcinomas ex pleomorphic adenoma in major and minor salivary glands. In none of our 12 tumors, however, could we find histologic evidence of a precursor or maternal mixed tumor. Nor did we have the impression that the carcinoma had 'over-run' a mixed tumor.

The spindle cells in these terminal duct carcinomas are quite suggestive of a myoepithelial cell component and electron-optic study of fresh tissue from the tumor of patient 9 demonstrated myoepithelial differentiation in the spindle cells. Should this be further substantiated, terminal duct carcinomas are likely related to the clear cell class of salivary neoplasia; specifically, the epithelial-myoepithelial carcinoma of intercalated ducts. As can be seen from Figure 12, however, the outer clear cell mantle, often glycogen-rich, of the clear cell carcinoma distinguishes it from the carcinomas of the present report (Batsakis, 1980a; Corio *et al.*, 1982; Donath *et al.*, 1972).

A two and one-half year follow-up period is not sufficient to be able to delineate the full biologic potential of terminal duct carcinomas. The apparent local control in our patients, over the short post-operative

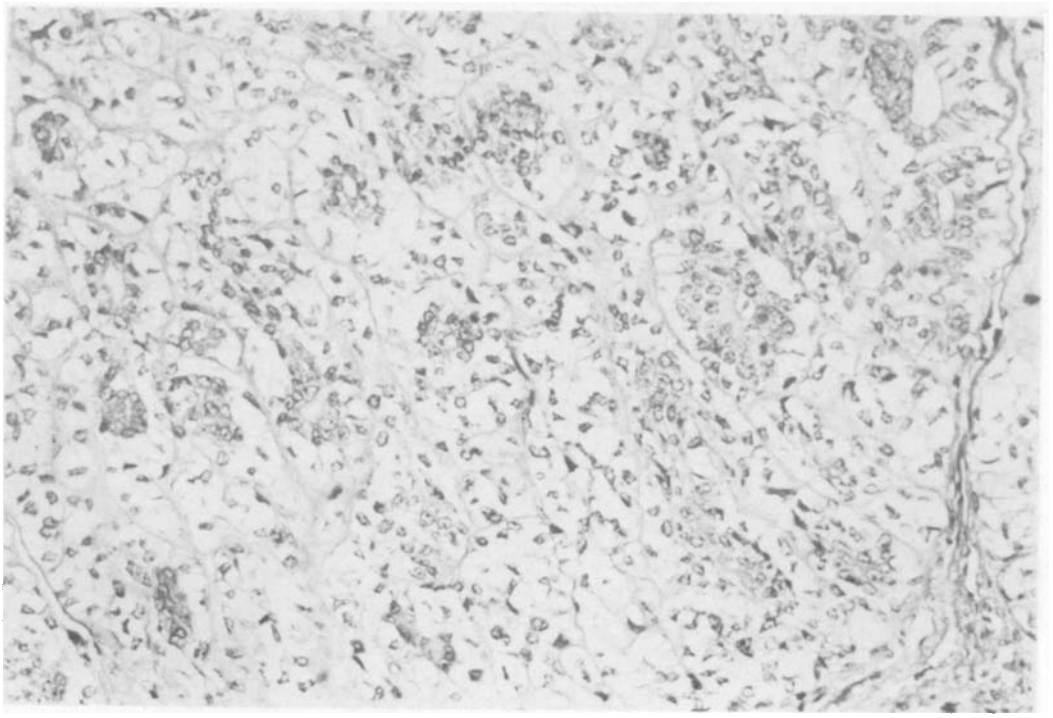

FIG. 12

Epimyoepithelial carcinoma of intercalated ducts. This clear cell carcinoma is likely related to the terminal duct carcinoma. Hematoxylin and eosin ×180.

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interval is likely deceptive. Based on the present series, we would judge terminal duct adenocarcinomas to have a clinical course not unlike adenoid cystic carcinomas.

Summary

A clinico-pathologic study of 12 patients, each harboring a hitherto not delineated adenocarcinoma of salivary origin is presented. The authors have designated this histologically unique carcinoma as 'terminal duct adenocarcinoma' in deference not only to its light-optic appearance, but also to a putative origin from the reserve cells (epithelial and myoepithelial) of the intercalated duct. The tumors' local invasive properties with extension into nerves and adjacent bone suggest their biologic behavior is like that of adenoid cystic carcinomas.

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